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REVIEWER

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 20 1986

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Review of Histopathology Tables submitted on 2,4-D

To: Ms Lin Vlier
Special Review
Registration Division TS-767C

From: Marcia van Gemert, Ph.D.
Head, Section III
Toxicology Branch, HED

M. van Gemert 10/16/86

Thru: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch, HED

10 20 86

Compound: 2,4-Dichlorophenoxyacetic acid

Tox Chem No.: 315

Registrant: Industry Task Force on 2,4-D Research Data

Accession No: 264983

Action Requested: Review submitted tables

The 2,4-D Task Force has submitted the revised histopathology tables according to our request as detailed in the Toxicology Branch memo of 6/20/86. Enclosed in this submission were:

1. The combined neoplastic and non-neoplastic tables which incorporated all the animals from the interim and terminal sacrifices, and the unscheduled deaths,

2. A set of tables which combined the histopathological findings by animal/organ system in order to assess if double counting was taking place,

3. A set of tables detailing the recent histopathology done to complete all the spinal cord sections,

4. The amended protocol concerning the original treatment of the spinal cord slides.

The submitted information and tables will be assessed in the order given above.

1. The combined neoplastic and non-neoplastic tables reveal

as detailed in the June 30, 1986 memo, an increase in kidney tubule cell pigment, an increase in transitional epithelial hyperplasia, microcalculi and fine cytoplasmic vacuolization. Also noted in the new tables is an increase in testicular granulomatous prostatitis as noted below.

Testes	non-neoplastic lesions				
	groups				
	1	2	3	4	5
granulomatous prostatitis	1	1	1	1	4

However, this finding does not change the NOEL set in the 6/30/86 memo.

2. The combined animal/organ system histopathology tables may indicate a slight correlation between the increased frequency of transitional cell hyperplasia and the presence of microcalculi in groups 4 and 5 in females and group 5 in the males.

	males					females				
	1	2	3	4	5	1	2	3	4	5
transitional epithalial hyperplasia	0	1	1	1	3	3	2	4	7	14
Microcalculi pelvis	2	3	4	8	12	21	14	16	26	39
animals with combined hyperplasia and microcalculi	0	1	0	0	2	2	2	3	6	13

The matter of kidney hyperplasia and its possible cause by microcalculi will be a matter for discussion at the Peer Review Committee meeting where the histopathology data will be presented.

3. The spinal cords were sectioned at the request of the Canadian government. These data are appended. The original protocol called for sectioning of only 10/sex/group. After examining the tables presented, there did not appear to be any increased incidence of astrocytomas associated with 2,4-D treatment.

4. The amended protocol, more clearly reflecting the original

histopathological treatment of the spinal cord slides is appended.

Conclusions:

A. The submitted data have not resulted in a change in the NOEL which was stated in the 6/30/86 memo to be

NOEL = 1 mg/kg/day
LEL = 5 mg/kg/day

B. The new combined animal/organ system histopathology tables indicate only a slight correlation between the increased frequency of transitional cell hyperplasia in the kidney and the presence of microcalculi. This will be a matter for the Peer Review Committee to discuss.

C. After reviewing the histopathology tables on the new sections there did not appear to be an increase in incidence of astrocytomas in the treated animals.

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
	SEX:	----------MALE----------					---------FEMALE---------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	60	60	60	60	60	60	60	60	60	60
** TOP OF LIST **											
CERV SPINAL CORD (CS)	NUMBER EXAMINED:	60	60	60	60	60	60	60	60	60	60
	NOT REMARKABLE:	56	58	59	59	58	60	58	60	60	60
--X-MONOCYTIC LEUKEMIA		2	1	0	1	2	0	1	0	0	0
--HEMORRHAGE		2	0	0	0	0	0	0	0	0	0
--SKELETAL MUSCLE REST		0	1	0	0	0	0	0	0	0	0
--KERATIN CYST		0	0	1	0	0	0	0	0	0	0
--I-ASTROCYTOMA, INVASIVE		0	0	0	0	0	0	1	0	0	0
THOR SPINAL CORD (TC)	NUMBER EXAMINED:	60	60	60	60	60	60	60	60	60	60
	NOT REMARKABLE:	59	59	60	59	57	59	59	59	59	60
--X-MONOCYTIC LEUKEMIA		1	1	0	1	2	0	1	0	0	0
--HEMORRHAGE		0	0	0	0	1	0	0	0	1	0
--NONSUPPURATIVE MYELITIS		0	0	0	0	0	0	0	1	0	0
--M-ASTROCYTOMA		0	0	0	0	0	1	0	0	0	0
LUN SPINAL CORD (LC)	NUMBER EXAMINED:	60	60	60	60	60	60	60	60	60	60
	NOT REMARKABLE:	55	58	60	59	58	60	59	60	59	60
--X-MONOCYTIC LEUKEMIA		3	2	0	1	2	0	0	0	1	0
--HEMORRHAGE		2	0	0	0	0	0	0	0	0	0
--KERATIN CYST		0	0	0	0	0	0	1	0	0	0
** END OF LIST **											

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2184-103

CORRECTION PAGES

Corrections to the final report, dated August 13, 1986, for pages 9, 31, 244, and 1587, are being submitted due to an error contained within these original pages.

Spinal cord sections from Group 2 female no. 23184 were erroneously reported as examined during the initially scheduled histopathologic evaluation. Corrections to the affected pages (page 9 - Methods; page 31 - Histopathologist's Report, page 244 - Summary Data, and page 1587 - Individual Data) are included herein.

As of this date, spinal cord sections from all animals have been examined histopathologically and the results are included elsewhere in this Amendment.

CORRECTION PAGE

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2184-103

trachea
esophagus
stomach
duodenum
ileum
jejunum
colon
cecum
adrenals
pancreas
liver
kidneys
urinary bladder
testes (with epididymides)
prostate
ovaries
uterus
spleen
mesenteric lymph nodes
skin with mammary gland from axillary region
sciatic nerve
sternum with marrow
skeletal muscle (attached to tibio-femoral joint)
spinal cord (cervical, thoracic, and lumbar)

Histopathology

All of the preserved tissues (except the spinal cord and coronal sections of the head) from all of the rats were embedded in paraffin, sectioned, stained with hematoxylin and eosin and examined microscopically. The spinal cord and three coronal sections of the head (including nasal cavity, paranasal sinuses, tongue, oral cavity, nasopharynx, and middle ear) were examined from the last 10 terminally sacrificed animals/sex/group.[a] Brain sections (including at lease one section from the forebrain, midbrain and hindbrain) were examined microscopically by the study pathologist and then read blind by a second pathologist. Following these examinations, remaining fixed brain tissue from each animal was processed and evaluated microscopically by the study pathologist; these observations were incorporated into the original findings to yield a composite incidence from both evaluations.

[a] Spinal cord sections were examined from 9 Group 2 females.

CORRECTION PAGE

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2184-103

PATHOLOGY SUMMARY
Unscheduled Deaths and Terminal Sacrifices

General Protocol

Six-hundred, six to seven week old Fischer 344 rats, 300 males and 300 females, were assigned computer generated random numbers and placed in one of five groups of 60 males and 60 females each. Group 1 served as the control group. Groups 2, 3, 4 and 5 served as the low-, mid-1-, mid-2-, and high-dose groups receiving 1, 5, 15 and 45 mg/kg/day respectively, of the test compound 2,4-Dichlorophenoxyacetic acid (2,4-D) in their diet.

Following 104/105 weeks of treatment, all surviving animals were anesthetized with a barbiturate, exsanguinated and necropsied with the following tissues collected and preserved in 10% neutral buffered formalin: brain, eyes with Harderian gland, pituitary, salivary gland, heart, thymus, thyroid with parathyroids, lungs, trachea, esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, adrenals, pancreas, liver, kidneys, urinary bladder, testes with epididymides, prostate (males), ovaries, uterine horns and body (females), spleen, mesenteric lymph nodes, skin, sciatic nerve, mammary gland, sternum with marrow, skeletal muscle, three levels of the spinal cord, nasal passage/cavity, nasopharynx, paranasal sinus, tongue, oral cavity, middle ear, and gross lesions. The above underlined tissues were weighed. The preserved tissues except for three levels of the spinal cord, nasal passage/cavity, nasopharynx, paranasal sinus, tongue, oral cavity and middle ear from unscheduled deaths and all but the last 10 terminal sacrificed animals in each dose group; and the preserved tissues except the lumbar spinal cord from the last 10 terminal sacrificed animals in each dose group were embedded in Paraplast●, sectioned at 5-6 μ, placed on glass slides and stained with hematoxylin and eosin and coverslipped and then examined by a board-certified veterinary pathologist.[a] In addition, all original brain sections were randomized and read "blind" by another Hazleton Senior Pathologist. Subsequent to these evaluations of three sections of brain per animal, three to five

[a] Spinal cord sections were examined from 9 Group 2 females.

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
SEX:		MALE					FEMALE				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		32	43	47	41	36	40	37	37	38	36
** TOP OF LIST **											
BRAIN (BR)	NUMBER EXAMINED:	32	43	47	41	36	40	37	37	38	36
	NOT REMARKABLE:	29	43	46	39	30	39	36	32	36	31
--VENTRAL COMPRESSION		0	0	1	2	1	1	0	3	1	4
--I-PITUITARY CARCINOMA		2	0	0	0	0	0	1	0	0	2
--B-GRANULAR CELL TUMOR		1	0	0	0	0	0	0	0	0	0
--M-ASTROCYTOMA		0	0	0	0	5	0	0	2	1	1
CERV SPINAL CORD (CS)	NUMBER EXAMINED:	10	10	10	10	10	10	9	10	10	10
	NOT REMARKABLE:	10	10	10	10	10	10	9	10	10	10
THOR SPINAL CORD (TC)	NUMBER EXAMINED:	10	10	10	10	10	10	9	10	10	10
	NOT REMARKABLE:	10	10	10	10	10	10	9	10	10	10
LUM SPINAL CORD (LC)	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
PITUITARY (PI)	NUMBER EXAMINED:	32	43	46	41	36	40	36	36	38	36
	NOT REMARKABLE:	21	27	24	28	24	18	13	14	24	16
--B-ADENOMA		8	8	17	10	9	16	14	17	8	11
--FOCAL HYPERPLASIA		1	5	3	0	1	1	2	0	2	4
--ANGIECTASIS		0	2	2	2	2	3	4	3	4	3
--M-CARCINOMA		2	0	0	0	0	0	1	0	0	2
--ABSCESS		0	1	0	1	0	0	0	0	0	0
--CYST(S)		0	1	0	0	0	2	2	2	0	0

CORRECTION PAGE

"Contains or relates to trade secrets, confidential or proprietary information of the industry task force on 2, 4-D research data."

HAZLETON LABORATORIES AMERICA, INC. *** PATH/TOX SYSTEM OUTPUT *** PRINTED: 02-SEP-8(
DEPARTMENT OF PATHOLOGY COMBINED CHRONIC TOXICITY AND ONCOGENICITY STUDY IN RATS WITH PAGE: 1587
2,4-DICHLOROPHENOXYACETIC ACID
INDIVIDUAL ANIMAL SUMMARY REPORT STUDY NUMBER: 218410T

ANIMAL NUMBER: R23184 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 02/25/85 STUDY DAY OF DEATH: 735 STUDY WEEK OF DEATH: 105 TERMINAL BODY WEIGHT: 235.4 GRAMS
DATE AND TIME OF NECROPSY: 02/25/85 10:50 PROSECTOR: JAN HAMANN RECORDER: BEVERLY SNYDER
POST-FIX WEIGHER: LINDA RUMBLE PATHOLOGIST: NOT REQUIRED BY PROTOCOL WEIGHER: DANNY THOMAS

THE FOLLOWING ORGANS WERE UNREMARKABLE AT NECROPSY:
ADRENALS (AD), BONE(S),OTHER (OB), BRAIN (BR), CECUM (CE), CERV SPINAL CORD (CS), CERVIX (CV), COLON (CO), CRANIAL CAVITY (CC), DIAPHRAGM (DP), DUODENUM (DU), ESOPHAGUS (ES), EYE(S) (EY), FEMOROTIBIAL JT (FT), FOOT/PAW (FP), HARDERIAN GL.(S) (HG), HEAD, CORONAL (HC), HEART (HT), ILEUM (IL), JEJUNUM (JE), KIDNEYS (KD), LIVER (LI), LUM SPINAL CORD (LC), LUNG (LU), LYMPH NODE,OTHER (LN), MAMMARY GLAND (MG), MESENTERIC L.N. (MS), MUSCLE(S),OTHER (OM), ORAL CAVITY (OC), ORGAN(S),GENERAL (OG), OVARIES (OV), PANCREAS (PA), PARATHYROIDS (PT), PERITONEAL CAVIT (PC), PREPUT/CLIT GL. (PG), SALIVARY GLD.(S) (SG), SCIATIC NERVE (SN), SKELETAL MUSCLE (SM), SKIN (SK), SKIN,OTHER (SS), SPLEEN (SP), STERNUM W/MARROW (SE), STOMACH (ST), SUBCUTANEOUS TIS (SQ), THOR SPINAL CORD (TC), THORACIC CAVITY (TA), THYMUS (TH), THYROID (TY), TRACHEA (TR), URINARY BLADDER (UB), UTERUS (UT), VAGINA (VA)

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
ADRENALS (AD), BRAIN (BR), CECUM (CE), COLON (CO), DUODENUM (DU), ESOPHAGUS (ES), EYE(S) (EY), HARDERIAN GL.(S) (HG), HEART (HT), ILEUM (IL), JEJUNUM (JE), MAMMARY GLAND (MG), MESENTERIC L.N. (MS), OVARIES (OV), PANCREAS (PA), PARATHYROIDS (PT), SALIVARY GLD.(S) (SG), SCIATIC NERVE (SN), SKELETAL MUSCLE (SM), SKIN (SK), SPLEEN (SP), STERNUM W/MARROW (SE), STOMACH (ST), THYROID (TY), TRACHEA (TR), URINARY BLADDER (UB), UTERUS (UT)

*** ALL ORGANS/TISSUES (REQUIRED TO BE HARVESTED PER THE STUDY PROTOCOL) WERE SAVED ***

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Chemical:	2-4,D
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